REMARKS

The Office Action of January 2, 2003 presents the examination of claims 1-5, 14-16, 18 and 19, the remaining claims being withdrawn from consideration in view of restriction of the claims. The agreement of the Examiner to later consider rejoinder of method of use claims limited in scope to allowed composition claims at the proper time is noted.

IDS

The Examiner indicates that no copy of the Ferrara reference listed on form PTO-1449 filed with the Information Disclosure Statement of June 20, 2001 was received. The Examiner should note that the IDS indicates that a copy was sent to the parent file 09/519,476. For the convenience of the Examiner, another copy is attached hereto, together with another form PTO-1449 for initialing by the Examiner.

Status of claims and support for amendments

Claims 14-16 are canceled herein, without prejudice to or disclaimer of the subject matter thereof. Claim 1 is amended to incorporate the transitional phrase of claim 14. Other amendments to claim 1 delete recitation of small fragments of the claimed sequence or are merely editorial in nature and clarify the language

f the claim in response to the Examiner's criticisms under 35 USC § 112, second paragraph.

Claim 18 is amended to recite dependence upon a pending claim.

New claims 31 and 32 recite one alternative embodiment of claim 1 ("(d)") and recites biological activity of the polypeptide encoded by the alternative embodiment. Support for this recitation can be found, e.g. at page 1, lines 18-21.

The title of the application is amended as required by the Examiner.

Rejections under 35 USC § 112, second paragraph

Claim 1 is amended to clarify the language objected to by the Examiner, thus obviating this rejection. Claim 14 is canceled, rendering the rejection of this claim moot.

Rejection under 35 USC § 112, first paragraph

Claims 2, 3, 15 and 16 stand rejected under 35 USC § 112, first paragraph, as allegedly unsupported by enabling disclosure in the specification. Claims 15 and 16 are canceled, rendering this rejection moot as to those claims. This rejection is respectfully traversed as it is applied to claims 2 and 3 (and 1).

The Examiner takes a position that the specification does not enable the skilled artisan to fully practice the invention as claimed in claims 2 and 3. In particular, the Examiner asserts

that undue experimentation would be required for one of ordinary skill in the art to find use for "nucleic acids encoding inoperative polypeptides"; a large number of which are said to be encompassed by claims 2 and 3 as there is no functional limitation associated with the variants in the claims. Applicants have noticed in preparing this response that the Examiner seems to have overlooked the alternative embodiment (d) in claim 1, now present in claim 31.

Applicants have presented new claim 31, reciting a 70% level of homology, to include a limitation that the variant nucleic acids encode a polypeptide retaining two biological activities associated with VEGF. Applicants submit that this amendment addresses the Examiner's basis for the instant rejection as applied to claims 1-3, now 31 and 32, and so it should be withdrawn.

Rejection over prior art

Claims 1-5, 14-16, 18 and 19 stand rejected under 35 USC § 102(b) as anticipated by Keck et al., U.S. Patent 5,240,848. Claims 14-16 are canceled, rendering the rejection moot as to these claims. This rejection is respectfully traversed as to the remaining claims 1-5, 18 and 19.

Keck discloses a polynucleotide that is 1195 nucleotides long and encodes a polypeptide having biological activity of increasing vascular permeability. The nucleic acid disclosed by Keck is plainly distinct from the presently claimed nucleic acid, which is

described in SEQ ID NO: 1 as being 426 nucleotides long. The nucleic acid of the present invention encodes a splice variant of VEGF, which is a protein having biological activities of inducing vascular endothelial cell proliferation and inhibiting apoptosis of vascular endothelial cells.

One isoform of VEGF isolated previously is 165 amino acids long (see, e.g. page 2, lines 12-13 of the specification). The VEGF variant of the present invention is an isoform 114 amino acids long and is encoded by the splice variant described as an embodiment of the present invention as SEQ ID NO: 1. The isoform of the present invention ("$VEGF_{114}$") retains the biological activities of inducing vascular endothelial cell proliferation and inhibiting apoptosis of vascular endothelial cells, albeit to a lower degree than the 165 amino acid isoform ("$VEGF_{165}$"). The data in Exhibit A attached[1] also show that the $VEGF_{114}$ isoform lacks the ability of $VEGF_{165}$ to promote sprouting of new blood vessels in an *in vitro* angiogenesis assay. Thus, the skilled artisan expects that the $VEGF_{114}$ isoform retains the ability to bind to the VEGF receptor on the surface of vascular endothelial cells and can act as an antagonist of some activities and as a partial agonist of other activities of VEGF (see page 35, lines 1-2 of the specification.

[1] Applicants are in the process of preparing a Declaration under 37 CFR § 1.132 to submit this evidence in testimonial form.

The nucleic acid disclosed by Keck is clearly distinguished from the nucleic acid claimed as the present invention. Accordingly, the rejection of claims 1-5, 18 and 19 over Keck should be withdrawn.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number below.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $205.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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2786-0177P
Attachments

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The title has been amended as follows:

Novel VEGF Nucleic Acid and Amino Acid Sequences

Claims 14-16 are canceled.

The claims have been amended as follows:

1. An isolated nucleic acid molecule comprising nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence of SEQ ID NO: 1;

(b) a nucleotide sequence encoding the amino acid sequence of SEQ ID NO. 2; and

~~(c) a nucleotide sequence encoding a portion of the amino acid sequence of SEQ ID NO: 2 and having at least 20 nucleotides~~;

~~(d) a nucleotide sequence having at least 70% identity to the sequence of SEQ ID NO: 1; and~~

~~(e)~~ (c) a nucleic acid sequence that is complementary to the nucleic acid sequence of SEQ ID NO: 1~~; and~~

~~(f) a nucleic acid sequence that is complementary to a portion of the nucleotide sequence of SEQ ID NO. 1 and having at least 20 nucleotides~~.

18. An expression vector comprising an isolated nucleic acid molecule of claim ~~14~~ 1that comprises a nucleotide sequence encoding the amino acid sequence of SEQ ID No: 2 or a nucleotide sequence that is complementary to a nucleic acid sequence encoding the amino acid sequence of SEQ ID No: 2; and control elements for expression of the nucleic acid molecule in a suitable host cell.

Claims 31 and 32 have been added.